REMARKS

Claim 1 has been amended to more definitely set forth the invention and obviate the rejections. Support for the amendment of claim 1 can be found in the specification on page 6, lines 7-13, and page 15, lines 23-24 (which provides support for the addition of "matrix-type" to claim 1), as well as page 16, lines 7-9 (which provide support for the prohibition of water in the composition of claim 1. This amendment is deemed not to add new matter. Claims 1-26 are in the application.

Reconsideration is respectfully requested of the rejection of claims 1-6, 11-15 and 20-26 under 35 U.S.C. 102(b), as being anticipated by Higo, et al. (USPN 5,733,900).

The cited Higo, et al. reference discloses a percutaneous administration base composition and medicinal composition for application thereon. The medicinal composition of Higo, et al. is a reservoir-type patch formulation containing water and lower alcohol as essential components, intended to promote the percutaneous absorption of a medicine with little irritation to the skin (see column 5, line 1).

In particular, Higo et al. disclose a percutaneous absorption formulation containing 20-70 wt% water and 15-40 wt% of moisture-retaining agent (see column 4, lines 7-12). Higo, et al. state that "if the content of the moisure-retaining agent is

less than 15% by weight in the composition, the composition will cause skin irritation", and "if the content of water is less than 20% by weight, the composition will cause skin irritation" (see column 3, lines 40-47). Thus, water and a humectant are taught as necessary components of the Higo, et al. composition.

The purpose of the present invention, however, is to improve the solubility of the basic drug in the **matrix-type** patch composition **which contains no water**, by forming ion pairs between the basic drug and the organic acid salt in the matrix-type patch formulation. It was unexpectedly discovered that inclusion of specified amounts of an organic acid and an organic acid salt into the matrix-type patch formulation, along with a basic drug in the form of an acid addition salt, in the absence of water, provides more stable ion pair formation than in a patch including the organic acid salt alone, and a quasi-stable state is obtained, which is capable of elevating skin permeability of the drug therein (see Specification, page 5, lines 17-27).

Importantly, it is stated that "[t]he patch formulation for external use according to the present invention is preferably a non-water soluble system, containing no water" (see Specification, page 16, lines 7-9). This condition is important to achieving the objects of the present invention, as ion pairs formed, based on the static interaction, will dissociate when water is present. Thus, in

contrast to the disclosure of Higo, et al., the present invention provides a **matrix-type** patch formulation **containing no water** for external use, comprising a basic drug, an organic acid, and an organic acid salt as essential components. Further, the effect of the organic acid in the present invention differs significantly from that of the cited **reservoir-type** patch formulation of the Higo, et al. reference containing water, which is now prohibited in amended claim 1 herein.

In view of the amendments to claim 1 herein, the deficiencies of the cited Higo, et al. reference pointed out above, as well as the arguments presented herein, it is believed that the Examiner would now be justified in no longer maintaining the rejection. Withdrawal of the rejection is accordingly respectfully requested.

Reconsideration is respectfully requested of the rejection of claims 1-26 under 35 U.S.C. §103(a) as being unpatentable over Higo, et al. (USPN 5,733,900) in view of knowledge in the art.

As stated above, the Higo, et al reference is concerned with a reservoir-type patch formulation which contains water, and fails to disclose a matrix-type patch formulation containing no water as claimed herein. In fact, Higo, et al. state that "[i]f the content of water is less than 20% by weight, the composition will cause skin irritation (see column 4, lines 46-47). This need for water in the composition of Higo, et al. is clearly

demonstrated in Table 1, which illustrates that superior results are obtained in the compositions of the Examples containing water (see Table 1, column 9, Examples 1, 5 and 6).

The present invention, however, provides a matrix-type patch formulation containing NO WATER, a basic drug, an organic acid and an organic acid salt. Further, as the Examiner has noted on page 3 of the instant Office Action, Higo, et al. fail to recite the claimed specific ratios and concentrations of the present invention.

The Examiner argues that the recitation of the specific ratios and concentrations are within the level of skill of one of ordinary skill in the art. However, if an Examiner seeks to rely upon a theory of chemistry for obviousness, he must provide evidentiary support for the existence and meaning of that theory. *In re Grose, et al.* 592 F2d 1161, 201 USPQ 57 (CCPA 1979). Unless the applicant questions the accuracy of a statement of the examiner unsupported by the art of record by requesting a Rule 107 affadavit, or by presenting evidence to contradict it, it will be accepted as true on appeal. *In re Fox* 471 F2d 1405, 176 USPQ 340 (CCPA 1957), *In re Shapleigh* 248 F2d 96, 115 USPQ 129 (CCPA 1957); *In re Lundberg, et al.* 244 F2d 543, 1113 USPQ 530 (CCPA 1957); MPEP 706.02(a).

It is respectfully submitted that as the composition of

Higo, et al. is NOT a matrix-type patch formulation containing no water, as described above and now claimed herein, the allegation that Higo, et al. provide the basis for the choice of the ratios and proportions claimed herein is unsupported by the showings of Higo, et al. Thus, it is respectfully requested that the Examiner provide new evidentiary support for the contention that the claimed concentrations are within the skill of one of ordinary skill in the art pertaining to matrix-type patch formulations containing no water (as Higo, et al. have been shown not to be of ordinary skill in the particular art claimed herein).

Further, with respect to the claimed proportions and ranges of concentrations claimed herein, if the proportions are critical to the properties of the novel product, they can render the product patentable even though the percentages of ingredients fall within the broad ranges of the prior art. *Becket v. Coe* 98 F2d 332, 38 USPQ 26 (CADC 1938); *In re Becket, et al.* 88 F2d 684, 33 USPQ 33 (CCPA 1937); *In re Arness* 95 F2d 344, 37 USPQ 217 (CCPA 1938). The fact that the percentages of the chemical components of a chemical compound fall within the general proportions of the reference does not preclude patentability where the disclosure of the specification is persuasive of the criticality of the claimed proportions. *Ex parte Selby* 153 USPQ 476 (POBA 1966); *In re Waymouth, et al.* 499 F2d 1273, 182 USPQ

290 (CCPA 1974).

In the present invention, Examples 1-6 were prepared comprising the matrix-type patch formulation of the present invention (i.e., a basic drug, an organic acid and an organic acid salt, in the claimed ratios). In addition, Comparative Examples 1-10 were prepared, which contained a basic drug, but variously lacked a component present in the instant invention. Each of these compositions was then tested to determine its crystallization (which alters the release characteristics and adhesive properties of a composition) and the percutaneous absorbability. The results of these tests are shown in Table 1, on page 24 of the Specification.

As illustrated in Table 1, it was unexpectedly discovered that by combining the basic drug, an organic acid and an organic acid salt in the claimed ratios and weight ranges, excellent percutaneous absorption, as well as formulation stability, was obtained, perhaps due to the synergistic effect of the claimed combination. In contrast, the Comparative Examples 1-10 showed overall poor results with regards to percutaneous absorption and formulation stability.

Proof of unobviousness of a therapeutically active mixture of compounds can be based on (1) broader therapeutic spectrum, (2) higher activity, (3) more extended of complete activity, (4)

improved tolerance, **(5) improved absorption**, (6) decreased toxicity, **(7) reduced sensitization**, (8) elimination of microbial resistance. Roditi, H. and Bossard, J. "The Patentability of Synergistic Association", 47 JPOS 40, 46-50 (1965).

It is respectfully submitted that the unexpectedly superior test results shown in Table 1 illustrate the criticality and unobviousness of the claimed proportions and ranges of the components of the present invention. Based on the teachings of the legal authorities cited above, it is thus believed that these showings clearly demonstrate unobviousness and patentability.

In view of the arguments and discussions herein, as well as the legal authorities cited above, it is believed that the Examiner would now be justified in no longer maintaining the rejection. Withdrawal of the rejection is accordingly respectfully requested.

In view of the foregoing, it is respectfully submitted that the application is now in condition for allowance, and early action and allowance thereof is accordingly respectfully requested. In the event there is any reason why the application cannot be allowed at the present time, it is respectfully requested that the Examiner contact the undersigned at the number listed below to resolve any problems.

Respectfully submitted,

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MARKED-UP VERSION OF AMENDED CLAIM 1:

1. (Twice Amended) A matrix-type patch formulation containing no water for external use, comprising:

a basic drug,

an organic acid; and

an organic acid salt as essential components.